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(54) Title: USE OF INSULIN-LIKE GROWTH FACTOR IN COMBINATION WITH INSULIN

(57) Abstract

The invention relates to a method for treating catabolic diseases other than diabetes, promoting growth, enhancing wound repair or treating gut disease in a mammal including the step of administering effective amounts of: insulin like-growth (IGF); and insulin. The invention also provides pharmaceutical and veterinary compositions and kits for these conditions.

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USE OF INSULIN-LIKE GROWTH FACTOR IN COMBINATION WITH INSULIN

This invention relates to the combined use of insulin-like growth factor and insulin in promoting growth, treating catabolic diseases including but not limited to cancer, and enhancing wound repair. The invention also relates to pharmaceutical and veterinary compositions useful for promoting growth, treating catabolic diseases and enhancing wound repair.

Insulin, insulin-like growth factor (IGF)-I and IGF-II share considerable sequence homology as indicated from their names. Nevertheless, insulin acts through a distinct receptor which has a low affinity for IGF-I or IGF-II, whereas IGF-I and IGF-II are considered to elicit their growth-stimulating responses through the type 1 IGF receptor. A second IGF receptor, the type 2 receptor, binds IGF-II but not IGF-I nor insulin with any significant affinity and may be involved in some cellular functions of IGF-II. The two growth-related receptors are distributed in mammals in a tissue-specific manner so that the insulin receptor is abundant in adipose tissue, liver and muscle while the type 1 IGF receptor has a high density especially in muscle, kidney and gut tissues but is absent in the parenchynal cells of liver and is barely detectable in adipose tissue.

Insulin, IGF-I and IGF-II all produce short-term metabolic effects and longer-term growth responses in their target tissues. Since the clinical importance of insulin is mostly associated with metabolic responses such as uptake of glucose and amino acids from blood, the inhibition of gluconeogensis or the promotion of lipid deposition through increases in lipogenesis and decreases in lipolysis, longer-term growth responses have sometimes been suggested to occur via the limited cross-reactivity of insulin with the type 1 IGF receptor. The opposite situation with the IGFs has also been proposed with their short-term metabolic ff cts postulated to occur through the insulin receptor. However, a number of inv stigations have been reported in which subjects, animals or cells with insulin resistance demonstrate normal responsiveness to IGF-I that includes short-term

metabolic effects. Examples of these reports include T. Sasaoka et al. Diabetes 37, 1515, 1988; J.A. Maasen et al. Eur. J. Biochem. 190, 553, 1990; R. Jacob et al. Am. J. Physiol. 260, E262, 1991; L. Rossetti et al. Diabetes 40, 444, 1991; H. Kuzuya et al. Diabetes 42, 696, 1993; and A-L. Usala et al. New Eng. J. Med. 327, 853, 1992. As these examples include cases with defects in the insulin receptor or insulin receptor signalling, it is clear that the responsiveness to IGF-I must have occurred through interaction between the growth factor and a receptor other than the insulin receptor, presumably the type 1 IGF receptor. Further evidence that IGF can replace insulin comes from experiments with streptozotocin-diabetic rats in which body weight gain and nitrogen balance can be restored to normal by insulin or by IGF-I (see for example F.M. Tomas et al. Biochem J. 291, 781, 1993).

The prior art also contains many examples whereby IGF can promote body weight gain and improve nitrogen balance or retard weight loss in rats that are not diabetic. Examples include normal animals (F.M. Tomas et al. J. Endocrinol. 137, 413, 1993), those made catabolic with food restriction (F.M. Tomas et al. J. Endocrinol. 128, 97, 1991), high doses of dexamethasone (F.M. Tomas et al. Biochem J. 282, 91, 1992), rats with acute or chronic renal failure (A.A. Martin et al. Am. J. Physiol. 261, F626, 1991), and those in which removal of a substantial portion of the small intestine has led to weight loss (A.B. Lemmey et al. Am. J. Physiol. 260, E213, 1991). In each of these situations the elicited improvements have been sustained by continual administration of IGF and are accompanied by high circulating levels of the growth factor. It is surprising, therefor, that IGF-I administration to human subjects with catabolic diseases generally leads only to a transient increase in circulating IGF-I and only a transient improvement in nitrogen balance or weight gain (S.A. Chen et al. 75th Ann. Meeting. Endocrinol. Society, abstract 1596, 1993).

Attempts have been made to overcome the transience of the effects following IGF-I administration to human subjects having catabolic conditions by the use of combination therapy with IGF-I plus growth hormone. Such a

combination treatment is successful in rodents (for example see US patent No. 5,126,324), but beneficial responses in disease conditions have not yet been demonstrated in human subjects.

It is an object of the present invention to overcome or at least alleviate one or more of the deficiencies of the prior art.

According to the present invention there is provided a method for the treatment of catabolic diseases in mammals including the step of administering to the mammal an effective amount of:

insulin-like growth factor (IGF), and

insulin.

Combination treatment with IGF-I or IGF-II plus insulin in catabolic conditions has not been evaluated in either experimental animals or human subjects. This lack of investigation occurred because prior art predicts that such a combination would exacerbate the hypoglycemic effects of the individual compounds irrespective of whether the IGF acts via the insulin receptor or the type 1 IGF receptor.

The term "insulin" as used herein includes both the natural and recombinantly produced pancreatic hormone. The term includes all mammalian sequences of the hormone and is limited only in that the material must demonstrate the expected biological activity of the hormone in the recipient. Therefore the term also applies to analogues of any mammalian insulin provided they are physiologically reactive.

The term "insulin-like growth factor" (IGF) as used herein is intended to include both natural and recombinant insulin-like growth factor-I (IGF-I) regardless of the sourc . The term is also intended to include both natural and recombinant insulin-like growth factor-II (IGF-II) regardless of the source. The term includes all mammalian sequences of IGF-I and IGF-II. The term is limited only in that the

material must demonstrate IGF activity in the recipient. Therefore the term also applies to physiologically active analogues of any mammalian IGF, including the analogues referred to in International Patent Applications PCT/AU86/00246, PCT/AU88/00485 and PCT/AU90/00210, the entire disclosures of which are incorporated herein by reference.

The term "effective amount" refers to amounts of insulin-like growth factor (IGF) and insulin, or sources thereof, capable of inducing the desired pharmaceutical or veterinary effect.

Preferably the active ingredients are suspended, dissolved or dispersed in a carrier. The carrier may be any solid or liquid that is non-toxic to the mammal and compatible with the active ingredient. Suitable carriers include liquid carriers such as normal saline and other non-toxic salts at or near physiological concentrations and dilute acids. Other forms such as aerosols or slow release pellets are also contemplated.

The combined treatment of the invention is also useful in promoting growth in mammals.

Accordingly in a further aspect of the invention there is provided a method for promoting growth in a mammal including the step of administering to the mammal an effective amount of:

insulin-like growth factor (IGF), and

insulin.

The invention also provides a pharmaceutical or veterinary composition including effective amounts of:

insulin-like growth factor (IGF), and

insulin.

The compositions of the invention may further include a pharmaceutically or veterinarily acceptable diluent, carrier or excipient therefore. The particular carrier or excipient employed will depend necessarily on the method of administration and could be readily chosen by a person skilled in the art.

The term "mammal" as used herein is intended to include, but is not limited to, human subjects, pigs, cattle, sheep, guinea pigs and rodents.

As used herein, the terms "catabolic disease", "catabolic states" and "catabolic conditions" are intended to describe wasting conditions that include but are not limited to, cancer, acute or chronic organ failure, AIDS, physical trauma, infection and anorexia. Diabetes is specifically excluded.

It is well known that poor wound repair is a secondary consequence of catabolic conditions (W.J. Temple et al. Ann. Surg. 187, 93, 1975). Accordingly the compositions of the present invention are expected to enhance wound repair in mammals.

Accordingly the invention further provides a method for enhancing wound repair in a mammal including the step of administering to the mammal an effective amount of:

insulin-like growth factor (IGF), and

insulin.

The present invention is the first to combine the use of insulin with IGF for the treatment of catabolic diseases or to promote growth. Specifically, growth can be promoted or catabolic diseases can be reversed or ameliorated by the administration of insulin in combination with an insulin-like growth factor (IGF). The present invention discloses the unexpected result that insulin and IGF act synergistically to reverse the catabolic stat .

Without wishing to be limited by theory it is believed that this synergism partly occurs through the restoration of food intake in experimental animals by the added insulin which in turn provides the nutrients required to reverse tissue catabolism. The present invention also discloses that the unexpected synergism between IGF and insulin leads to a more balanced reversal of the catabolic state in which insulin predominantly increases growth of muscle as well as fat deposition, while IGF predominantly increases the growth of certain non-carcass tissues such as those of the gastrointestinal tract.

The unexpected synergism between IGF and insulin to promote the growth of body tissues also has application for the treatment of gut disease especially because insulin partly acts through the restoration of food intake while IGF separately increases gut growth and function as described in International Patent Application PCT/AU91/00031, the entire disclosure of which is incorporated herein by reference.

The term "gut disease" refers to digestive or absorptive disorders of any region of the gastrointestinal tract as well as inflammatory bowel diseases and mucositis.

Accordingly the invention further provides a method for treating gut disease including the step of administering to a mammal an effective amount of:

insulin-like growth factor (IGF),and

insulin.

The materials of the present invention may be administered by any means or pharmaceutical compositions that achieve their intended purpose. For example, administration of the materials of the present invention may be by subcutaneous, intravenous, intramuscular, intraperitoneal or transdermal routes.

The amount of IGF administered to th mammal will depend on the type of mammal, the age, health status and weight of the recipient, the mode of

administration and frequency of treatment, whether IGF-I, IGF-II or an IGF analogue is the chosen material, and the concurrent insulin treatment selected. Generally a daily dosage of IGF from 0.01 to 5.0 mg/kg body weight is effective.

The amount of insulin administered to the mammal will depend on the type of mammal, the age, health status and weight of the recipient, the mode of administration and frequency of treatment, and the concurrent IGF treatment selected. Generally a daily dosage of insulin from 0.01 to 2.0 mg/kg body weight is effective.

Preferably the insulin and IGF are administered over a period of between 1 and 60 days. The sources of insulin-like growth factor and insulin may be administered to the mammal as a composition which includes the IGF and insulin, or the IGF and insulin may be administered to the mammal separately. The IGF may be administered at the same time as, before or after the administration of the insulin.

Accordingly in another embodiment the invention provides a kit for treating a catabolic disease promoting growth, enhancing wound repair or treating gut disease in a mammal, said kit including:

(a) a pharmaceutical or veterinary composition including insulin and a pharmaceutically or veterinarily acceptable diluent, carrier or excipient therefor, and

(b) a pharmaceutical or veterinary composition including insulin-like growth factor (IGF) and a pharmaceutically or veterinarily acceptable diluent, carrier or excipient therefor.

The kit may further include means for administering components (a) and (b) to th mammal, such as syringe, infusion apparatus or the lik .

The methods and compositions of the present invention for enhancing growth in a mammal are suitable for the treatment of different species and at different developmental stages. For example, the combined insulin and IGF treatment may be used in suckling pigs or at the finisher stage.

The methods and compositions of the present invention for treating catabolic conditions are suitable for a wide range of such states. For example, the combined insulin plus IGF treatment may be used in cancer-bearing subjects or experimental animals, in conditions of acute or chronic organ failure, in physical trauma or prolonged infection. Since the methods of the invention are direct d to the catabolic state and not to the condition itself, the methods and compositions are expected to be capable of being utilized to treat all conditions resulting in catabolic states.

Examples

The benefits and parameters of the present invention will now be more fully described with reference to the accompanying examples. It should b understood, however, that the following description is illustrative only and should not be taken in any way as a restriction of the generality of the foregoing description.

Examples 1 to 4 described below illustrate the use of the combination treatment of the present invention to restore host weight gain in tumour-bearing rats. In the absence of treatment this example shows body weight gain over a 7-day period, but all the weight gain is tumour.

Insulin alone produces a modest increase in tumour-free body weight and enhances food intake. IGF has little effect on tumour-free body weight but inhibits food intake. A synergistic response is evident when insulin and IGF are co-administered, since the improved food intake licited by insulin alone is maintained while the tumour-fr e body weight gain is substantially greater. The synergy is also evident in the distribution of retained nitrogen in the tissues of the host.

Specifically, insulin alone increases growth of the muscle, skeleton and fat components that make up the carcass, IGF stimulates growth of non-carcass tissues, while the combination treatment produces balanced growth of the carcass and non-carcass body components. In this example, as with the application to enhance growth in non-catabolic states, plasma insulin concentrations are depressed by the administration of IGF alone.

Insulin and IGF-I have differential effects on the individual organs. Specifically, insulin but not IGF-I increases fat stores and skin weight but decreases spleen weight and tends to decrease kidney weight; IGF-I increases spleen, kidney and gut weights and decreases the weight of fat stores, while the combination treatment produces the desired increases in all tissues.

Example 1

Synergistic effects of IGF and insulin on growth in tumour-bearing rats

Female Dark Agouti rats (180 g body wt.) were held in cages at 25°C under controlled lighting (12 h-dark/12h-light cycle). The rats were fed on a commercial chow diet prior to implantation with a mammary adenocarcinoma. After implantation by subcutaneous injection of a cell suspension into each flank the tumour grows to 15% of host body weight in 2-3 weeks (A. Rofe et al. Biochem. J. 233, 485, 1986). Experiments were conducted over a 6 or 7 day period, during which time the tumour normally grows from 5% to 15% of body wt. Six rats were included in each experimental group. When the tumour had grown to 5% of body weight, as assessed by calliper measurement, mini-osmotic pumps containing the appropriate materials were implanted subcutaneously in the supra-scapular region.

There were 4 groups treated for 7 days, with each rat receiving two pumps: (1) vehicle + v hicle; (2) insulin, 100μg/day, + LR^3IGF-I vehicle; (3) LR^3IGF-I, 200μg/day, + insulin vehicle; (4) insulin, 100μg/day, + 10 LR^3IGF-I, 200μg/day.

Food and water intake and body weights were recorded daily. Tumour dimensions were measured by callipers at the start and mid-point of peptide infusion. Urine and faeces were collected daily from 2 days before pump insertion and stored at -20°C before analysis.

At the end of the experiment the rats were stunned and decapitated, and trunk blood was collected into a heparinized tube. The tumour on the right flank was then rapidly exposed, and a section was excised and frozen. The pelt, remaining tumour tissue and the visceral organs were then removed and weighed before being discarded. The musculo-skeletal remainder, designated as the carcass, was stored at -20°C for later analysis.

Food intake, tumour-free body weight gain, nitrogen balance and tumour burden are shown in the table:

Food intake and growth in tumour-bearing rats receiving IGF and/or insulin treatment

Values are means ± SEM for 6 animals in each group: **P<0.01; ***P<0.001 versus vehicle-treated control rats

Treatment	Dose (μg/day)	Food intake (g/day)	Tumour-free body-weight gain (g)	Nitrogen balance (mg/day)	Tumour burden (g/kg body wt)
Vehicle	0	13.0±0.2	-3.1±1.9	81±11	156±6
Insulin	100	19.0±0.5***	19.1±1.7***	110±8	115±6**
LR^3IGF-I	200	12.0±0.6	-1.1±4.7	142±10**	203±6***
Insulin + LR^3IGF-I	100+200	21.3±0.9***	37.9±1.5***	215±13***	151±9

Insulin and the IGF analogue LR^3IGF-I (as described in US patent 5,330,971 to the Applicants) produced distinct responses. Insulin significantly stimulated food intake, tumour-free body weight gain and reduced the tumour burden, while

LR^3IGF-I improved nitrogen balance, increased tumour burden and slightly decreased food intake. Surprisingly the combination treatment of insulin plus LR^3IGF-I synergistically increased the tumour-free body weight gain and the nitrogen balance well above the individual treatment values, while the tumour burden was unchanged from the control group. Accordingly this experiment demonstrates the usefulness of the combination treatment in the catabolic state induced by a rapidly growing tumour.

Example 2

Synergistic effects of IGF and insulin on body composition in tumour-bearing rats

This experiment was carried out exactly as described in Example 1. The table shows the tumour-free nitrogen accumulation in the rats over the seven day period as well as the proportions of this gain that are in carcass and non-carcass tissues.

Distribution of retained nitrogen in the tissues of rats implanted with a mammary adenocarcinoma and receiving vehicle, insulin, LR^3IGF-I or a combination treatment

Values are means ± SEM for 6 animals in each group

Treatment	Tumour free N gain (mg/d)	Carcass N gain (mg/d)	Non-Carcass N gain (mg/d)
Vehicle	8.4±6.9	-3.0±5.9	11.4±7.6
Insulin (100μg/d)	58.5±7.8	49.9±7.1	8.6±5.4
LR^3IGF-I (200μg/d)	36.2±11.1	-25.3±13.5	61.6±9.4
Insulin+ LR^3IGF-I	123.6±9.7	60.1±6.8	63.5±14.2

Both insulin and the IGF-I analogue stimulate tumour-free nitrogen gain. The tumour free nitrogen gain in the combined treatment was significantly greater ($p<0.001$) than the gain in either the insulin-treated or the IGF-treated group. Surprisingly, however, all the gain produced by insulin was in carcass tissues while all the gain produced by IGF-I was in non-carcass tissues. The combined treatment produced approximately equal increases in the carcass and non-carcass nitrogen.

A balanced reversal of the catabolic state has therefor been achieved.

Example 3

Direct measurements of nitrogen accumulation in all tissues of tumour-bearing rats with similar food intakes confirm synergistic effects of IGF and insulin on body composition

This experiment was carried out as described in Example 1 except that the dosage of insulin was reduced by one half to 50μg/rat/day and the dosage of LR^3IGF-I was reduced by one quarter to 150μg/rat/day. In addition, no tissues were discarded and nitrogen accumulation was directly measured in all tissues.

Dosage of insulin was reduced to circumvent the substantial rise in food intake observed in Example 1 during insulin infusion with the objective to separate the effects of insulin from nutrient intake. Food intakes of treated rats in this experiment remained within 15% of control rats.

Retention and distribution of nitrogen directly measured in the tissu s of rats implanted with a mammary adenocarcinoma and receiving v hicl , insulin LR^3IGF-I or a combination treatment.

Values are means ± SEM for 6 animals in each group

Treatment	Tumour free N gain (mg/d)	Carcass N gain (mg/d)	Non-Carcass N gain (mg/d)
Vehicle	11.5±4.8	8.8±5.1	2.8±3.8
Insulin (50μg/d)	33.0±5.6	14.2±3.3	18.8±3.2
LR^3IGF-I (150μg/d)	-0.2±9.0	-27.9±6.8	27.7±2.6
Insulin+ LR^3IGF-I	50.5±8.5	23.9±2.4	26.7±6.2

At these lower doses of hormone infusion insulin alone but not LR^3IGF-I alone stimulated tumour-free nitrogen gain. Insulin stimulated nitrogen gain in both carcass and non-carcass tissues whereas LR^3IGF-I stimulated gain in non-carcass tissues at the expense of carcass tissues. The combined treatment produced a much higher increase in the carcass nitrogen gain to match that of the LR^3IGF-I effect in non-carcass tissues resulting in a balanced increase in both tissues and a synergistic response in total tumour-free tissues.

Under conditions of lower hormone dosage and blunted changes in food intake the combined infusion achieved a balanced reversal of the catabolic state.

Example 4

Synergistic effects of IGF and insulin on specific organ weights in tumour-bearing rats.

The measurements in this example are the organ weights obtained when the exp rimental animals in Examples 2 and 3 were killed. Weights are expressed as grams wet weight of tissue per kilogram of body weight after the tumour weight had been subtracted.

Organ Weights (g/kg tumour-free body weight)

Values are means ± SEM for 6 animals in each group

Example	Treatment	Kidneys	Spleen	Omental fat	Skin	Empty Gut
2	Vehicle	6.88±0.08	2.83±0.07	-	153.6±3.6	34.3±0.9
	Insulin (100µg/d)	6.65±0.15	2.13±0.05+	-	157.8±1.6	35.3±1.0
	LR^3IGF-I (200µg/d)	8.84±0.14*	4.39±0.09*	-	152.3±2.4	45.0±1.0*
	Insulin+ LR^3IGF-I	7.73±0.13*	3.24±0.16*	-	155.6±1.9	47.1±0.5*
3	Vehicle	7.76±0.12	3.38±0.07	15.0±0.5	157.2±2.9	26.7±0.4
	Insulin (50µg/d)	7.41±0.09	2.89±0.09+	16.2±0.6	168.7±3.6*	27.6±1.5
	LR^3IGF-I (150µg/d)	9.55±0.18*	4.68±0.04*	10.3±0.4+	151.3±2.7	35.1±0.9*
	Insulin+ LR^3IGF-I	8.79±0.39*	3.79±0.21*	16.0±0.5	173.8±5.1*	36.8±1.4*

*P<0.05 versus respective vehicle groups for increases in tissue weight;

+P<0.05 versus respective vehicle groups for decreases in tissue weight.

The results of tissue weight comparison in the two experiments show a consistent pattern: Thus (a) kidney weights tend to be lower in insulin-treated animals (not statistically significant) but are significantly higher in LR^3IGF-I-treated and combination-treated animals; (b) spleen weights are lower in insulin-treated rats but are higher in IGF-I-treated and combination-treated rats; (c) Omental fat, measured only in Example 3, was substantially reduced in LR^3IGF-I-treated animals but restored to normal when insulin was included with LR^3IGF-I; (d) in Example 3 the skin (pelt) weight was increased by insulin and the combined treatment; a similar but non-significant trend occurred in Example 2; (e) The weight of the empty gut was unaffected by insulin but substantially increased in the LR^3IGF-I-treated and combination-treated groups.

These measurements of organ weight show that unlike insulin or LR^3IGF-I alone, the combination treatment leads to increases in the weights of the tissues shown in the table or blocks the fall in weight caused by one of the factors. Such changes are appropriate for improved growth in the catabolic state or to support overall growth. The effects on gut weight are particularly beneficial for the treatment of gut disease.

Finally it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

CLAIMS

1. A method for the treatment of catabolic diseases in mammals including the step of administering to the mammal effective amounts of:

insulin-like growth factor (IGF), and

insulin.

2. A method according to claim 1 wherein the catabolic disease is select d from cancer, acute organ failure, chronic organ failure, AIDS, physical trauma, infection and anorexia.

3. A method according to claim 2 wherein the insulin and insulin-like growth factor (IGF) are administered intravenously, subcutaneously, intramuscularly, transdermally or intraperitoneally.

4. A method according to claim 3 wherein the insulin is administered in an amount of from 0.01 to 2.0 mg/kg body weight/day and the insulin-like growth factor is administered in an amount from 0.01 to 5.0 mg/kg body weight/day for a period of 1 to 60 days.

5. A method for promoting growth in a mammal including the step of administering effective amounts of:

insulin-like growth factor (IGF), and

insulin.

6. A method according to claim 5 wherein the insulin and insulin-like growth factor are administered intravenously, subcutaneously, intramuscularly, transdermally or intraperitoneally.

7. A method according to claim 6 wherein the insulin is administer d in an amount of from 0.01 to 2.0 mg/kg body weight/day and the insulin-like growth

factor is administered in an amount from 0.01 to 5.0 mg/kg body weight/day for a period of 1 to 60 days.

8. A method for enhancing wound repair in a mammal including the step of administering effective amounts of:

insulin-like growth factor (IGF), and

insulin.

9. A method according to claim 8 wherein the insulin and insulin-like growth factor are administered intravenously, subcutaneously, intramuscularly, transdermally or intraperitoneally.

10. A method according to claim 9 wherein the insulin is administered in an amount of from 0.01 to 2.0 mg/kg body weight/day and the insulin-like growth factor is administered in an amount from 0.01 to 5.0 mg/kg body weight/day for a period of 1 to 60 days.

11. A method for the treatment of gut disease in a mammal including the step of administering effective amounts of:

insulin-like growth factor (IGF), and

insulin.

12. A method according to claim 11 wherein the insulin and insulin-like growth factor are administered intravenously, subcutaneously, intramuscularly, transdermally or intraperitoneally.

13. A method according to claim 12 wherein the insulin is administered in an amount of from 0.01 to 2.0 mg/kg body weight/day and the insulin-like growth factor is administered in an amount from 0.01 to 5.0 mg/kg body weight/day for a p riod of 1 to 60 days.

14. A pharmaceutical or veterinary composition including effective amounts of insulin-like growth factor (IGF), and insulin.

15. A composition of claim 14 further including a pharmaceutically or veterinarily acceptable diluent, carrier or excipient.

16. A kit for treating catabolic diseases, promoting growth, enhancing wound repair or treating gut disease in a mammal, said kit including:

(a) a pharmaceutical or veterinary composition including insulin and a pharmaceutically or veterinarily acceptable diluent, carrier or excipient therefor, and

(b) a pharmaceutical or veterinary composition including a source of insulin-like growth factor (IGF) and a pharmaceutically or veterinarily acceptabl diluent, carrier or excipient therefor.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00422

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 38/28, 38/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6: A61K 038/28, 038/30 IPC5 A61K 037/26, 037/02 + KEYWORDS

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CASM: (INSULIN()LIKE()GROWTH()FACTOR# OR IGF:)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 93/04691 A1(LIFE MEDICAL SCIENCES INC) 18 March 1993 (see pages 8,9)	14-16 1-13
X	EP 0561 330 A1 (LIEDTKE, RAINER K., Dr) 22 September 1993 (whole document)	1-16
X Y	AU-A 57908/90 (UNIVERSITY OF DUNDEE) 3 January 1991 (whole document)	14-16 1-13
Y	WO 92/20367 A1 (AMLYN PHARMACEUTICALS INC) 23 May 1992 (whole Document)	1-16

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1995	10 OCTOBER 1995

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00422

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Patent Abstracts of Japan, C1076 Page 159 JP 5-43453 A (SUMITOMO PHARMACEUTCO LTD) 23 February 1993 (whole abstract)	1-16
Y	WO 93/00110 A1 (GENENTECH, INC) 16 June 1992 (whole document)	1-16
Y	WO 94/16723 A1 (SYNERGEN INC) 25 January 1994 (whole document)	1-16
Y	WO 94/04030 A1 (CELTRIX PHARMACEUTICALS INC) 26 August 1993 (whole document)	1-16
Y	WO 93/10806 A1 (INSTITUTE OF MOLECULAR BIOLOGY INC) 4 November 1992 (whole document)	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 95/00422

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	93 04691	AU	25879/92	EP	650366	JP6510453	
EP	561330	DE	4208552	EP	561330	JP	6316530
AU	57908/90	US	5091173	CA	2020053	EP	405656
		JP	3128310				
WO	92 20367	AU	16873/92	AU	20115/92	CA	2082928
		EP	533898	JP	5507943		
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		US	5202119				
WO	94 16723	AU	60937/94				
WO	94 04030	EP	661990	WO	94 04030	US	5407913
WO	93 10806	AU	30668/92	EP	615452	JP	7501340
JP	5-43453	NO	FAMILY	MEMBERS			

END OF ANNEX